

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/051307

International filing date (day/month/year)
30.06.2004

Priority date (day/month/year)
30.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07D471/04, A61K31/4745, A61P25/00, A61P15/00, A61P3/10

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/051307

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/051307

Box No. III Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 18-20

because:

- ☒ the said international application, or the said claims Nos. 18-20 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
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International application No.
PCT/EP2004/051307

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-20
Industrial applicability (IA)	Yes: Claims	1-17
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
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AUTHORITY (SEPARATE SHEET)**

International application No.

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1) Reference is made to the following documents:

- D1: WO 03/051877 A
D2: WO 03/014117 A
D3: WO 03/014116 A
D4: WO 02/48144 A
D5: US-A-5 965 575
D6: DIAZ M. ET AL.: "Synthesis of Lamellarins I and K by [3+2] Cycloaddition of a Nitron to an Alkyne" SYNLETT, vol. 7, 2001, pages 1164-1166, XP001155819
D7: MEYER H: "HETEROCYCLEN AUS NITROALKENEN, I.-//PYRROLE DURCH CYCLISIERENDE MICHAEL-ADDITION VON ENAMINEN//HETEROCYCLES FROM NITROALKENES, I.- PYRROLES VIA MICHAEL ADDITION OF ENAMINES" LIEBIGS ANNALEN DER CHEMIE, VERLAG CHEMIE GMBH. WEINHEIM, DE, no. 9, 1981, pages 1534-1544, XP001068958 ISSN: 0170-2041
D8: HERSHENSON: "Synthesis of Ring-Fused Pyrroles. II. 1,3-Dipolar Cycloaddition Reactions of Murchisonone Derivatives Obtained from Tetrahydroisoquinoline-1-carboxylic Acids" J.ORG.CHEM., vol. 40, no. 6, 1975, XP002302597

2) Reference to section III

Claims 18-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3) Novelty (Reference to section V)

D1-D4 and D7 disclose substituted pyrrolo[2.1-a]isoquinolines which are excluded from the subject-matter of the present application by means of a proviso.

D5 describes N-aryl piperidine compounds (cf. D5 on columns 1-2, and in particular the last two definitions of the group A at the beginning of column 2), which do not fall into the definition of present formula (I); the teaching of D5 differs in fact from the subject-matter of the present application in the definition of the Ar substituent (cf. on the contrary the definitions of current groups R6 and R7).

D6 refers to the synthesis of lamellarins I and K: in particular, formulas 9a and 9b on page 1165 of D6 differ from the subject-matter of the present application in the presence of a

-COOEt group, which is absent in the definition of the current R6 group.

D8 describes some ring-fused pyrroles, which however do not fall into the definition of present claims (cf. in particular formulas 6a, 6b, 7 and 8 of D8 and the definitions of current substituents R7 and R8).

Accordingly, the subject-matter of present claims 1-20 meets the criteria of Article 33(2) PCT.

4) Inventive step (Reference to section V)

Each of the documents D1-D4, disclosing 2-substituted pyrrolo[2.1-a]isoquinolines derivatives as PDE10 inhibitors, may be considered to represent the closest state of the art.

The problem to be solved by the present application may therefore be regarded as the provision of further PDE10 inhibitors, which can be used for the treatment of disorders of the central nervous system, of diabetes or in the regulation of fertility.

Pyrrolodihydroquinoline derivatives are known from D1-D4 to possess a PDE10 inhibitory activity and from D5 it is known that they may be employed in the treatment of psychiatric disorders (cf. column 2 of D5, lines 53-63).

Consequently, the person skilled in the art, when trying to solve the above-mentioned technical problem, would obviously seek for an alternative in documents D1-D5.

Said skilled person would thus try and modify the substituents on the pyrrolodihydroisoquinoline ring in order to provide further PDE10 inhibitors and would reasonably expect that the provided compounds also demonstrate the same activity.

When comparing the substituent pattern known from D1-D5 with the present one, it seems that compounds claimed in the present application do not show any inventive step or any unexpected effects or properties over documents D1-D4.

Consequently, the subject-matter of current claims 1-20 does not meet the requirements set forth in Article 33(3) PCT.

5) Industrial applicability (Reference to section V)

For the assessment of the present claims 18-20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for

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International application No.

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example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6) Further observations (Reference to section VIII)

The relative expression "predominantly fluorine-substituted 1-4C-alkoxy" used in the claims has no well-recognised meaning and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).